Search Strategy

FILE 'USPATFULL' ENTERED AT 18:28:35 ON 14 NOV 2001

		E	CATANIA ANNA P/IN
		E	LIPTON JAMES M/IN
L33	3	S	E3
L34	4255	S	(TRIPEPTIDE OR TRIDECAPEPTIDE OR MSH OR MELANOCYTE STIMULATIN
L35	6	S	L34 AND (KPV OR LYSINE-PROLINE-VALINE)
L36	4	S	L35 NOT L33
L37	466	S	L34 AND (ANTIBACTERIAL OR ANTIMICROBIAL)
L38	123	S	L37 AND (MSH OR MELANOCYTE)
L39	13	S	L38 AND (TRIPEPTIDE OR TRIDECAPEPTIDE)
L40	11	S	L39 NOT L35

FILE 'MEDLINE' ENTERED AT 18:34:18 ON 14 NOV 2001

		E	CATANIA A P/AU
		E	CATANIA A/AU
L41	176	S	E3 OR E7
L42	7	S	L41 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L43	3	S	L41 AND (ANTIMICROBIAL OR ANTIBACTERIAL)
		E	LIPTON J M/AU
L44	236	S	E3
L45	7	S	L44 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L46	0	S	L45 NOT L42
L47	3	S	L44 AND (ANTIBACTERIAL OR ANTIMICROBIAL)
L48	0	S	L47 NOT L43
L49	5726	S	(MSH OR MELANOCYTE STIMULATING HORMONE)
L50	3	S	L49 AND (ANTIBACTERIAL OR ANTIMICROBIAL)
L51	0	S	L50 NOT L41
L52	1652	S	L49 AND INHIBIT?
L53	19	S	L52 AND INFECTION

L33 ANSWER 1 OF 3 USPATFULL
92:86953 Antipyretic and anti-inflammatory lys pro val compositions and method of use.
Lipton, James M. , 10662 Royal Springs Dr., Dallas, TX, United States 75229
US 5157023 19921020
APPLICATION: US 1991-672965 19910321 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An antipyretic tripeptide, having the amino acid sequence lysine-proline-valine, and a method for utilizing the tripeptide to reduce fever and inflammation in mammals are disclosed. The tripeptide can either be isolated from natural sources or chemically synthesized. A "protected" tripeptide having greater antipyretic potency and duration of action is also disclosed. The "protected" tripeptide contains an acyl group, such as an acetyl or a dibenzyl oxy carboxyl group, at its amino terminals and is amidated or esterified at its carboxyl terminals. Further, improved antipyretic potency and direction of action can be achieved through the co-administration of copper salts with the tripeptide.

CLM What is claimed is:
1. A pharmaceutical composition comprising an amount of a tripeptide having the formula Lys-Pro-Val that is effective to treat pyrexia or an amount effective to treat inflammation, the composition further comprising an amount of a copper salt that is effective to enhance the antipyretic action of said tripeptide.

2. The pharmaceutical composition of claim 1, wherein the tripeptide is a protected tripeptide, being diacylated at its amino terminus, or esterified or amidated at its carboxyl terminus.

3. The pharmaceutical composition of claim 2, wherein the tripeptide is diacetyl-lysine-proline-valine-NH.sub.2.

4. The pharmaceutical composition of claim 1, wherein the copper salt comprises copper chloride.

5. A method for the treatment of pyrexia in a mammal comprising administering to said mammal a composition comprising an effective amount of a tripeptide having the formula Lys-Pro-Val.

6. The method of claim 5, wherein the tripeptide is a protected tripeptide, being acylated at its amino terminus, or esterified or amidated at its carboxy terminus.

7. The method of claim 6, wherein the tripeptide is diacetyl-lysine-proline-valine-NH.sub.2.

8. The method of claim 6, wherein the tripeptide is dibenzyloxycarbonyl-lysine-proline-valine-dibenzylester.

L33 ANSWER 2 OF 3 USPATFULL
91:52531 Antipyretic and anti-inflammatory peptides.
Lipton, James M. , 10662 Royal Springs Drive, Dallas, TX, United States 75229
US 5028592 19910702
APPLICATION: US 1988-229331 19880805 (7)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An antipyretic tripeptide, having the amino acid sequence lysine-proline-valine, and a method for utilizing the tripeptide to reduce fever and inflammation in mammals are disclosed. The tripeptide can either be isolated from natural sources or chemically synthesized. A "protected" tripeptide having greater antipyretic potency and duration of action is also disclosed. The "protected" tripeptide contains an acyl group, such as an acetyl or a dibenzyl oxy carboxyl group, at its amino terminals and is amidated or esterified at its carboxyl terminals. Further, improved antipyretic potency and direction of action can be achieved through the co-administration of copper salts with the tripeptide.

CLM What is claimed is:

1. A method for the treatment of inflammation in an individual comprising administering to the individual a pharmaceutical composition which includes an anti-inflammatory amount of a peptide other than alpha-MSH, said peptide being 3 to 13 amino acids in length and including the tripeptide sequence Lys-Pro-Val, or a biologically functional equivalent of such a peptide.

2. The method of claim 1 wherein the peptide is the tripeptide Lys-Pro-Val.

3. The method of claim 2 wherein the Lys-Pro-Val tripeptide is protected at its amino or carboxy terminus.

4. The method of claim 3 wherein the protected tripeptide is acylated at its amino terminus or amidated at its carboxy terminus.

5. The method of claim 4 wherein the protected tripeptide is acetylated at its amino terminus and amidated at its carboxy terminus.

6. The method of claim 2 wherein the individual is administered from about 0.2 to about 3.5 mg tripeptide/kg body weight/day.

L42 ANSWER 1 OF 7 MEDLINE
2001166842 Document Number: 21166411. PubMed ID: 11268348. The neuropeptide alpha-MSH in host defense. ***Catania A*** ; Cutuli M; Garofalo L; Carlin A; Airaghi L; Barcellini W; Lipton J M. (Division of Internal Medicine, Ospedale Maggiore di Milano IRCCS, Via F. Sforza 35, 20122 Milano, Italy.. Anna.Catania@unimi.it) . ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2000) 917 227-31. Ref: 28. Journal code: 5NM; 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB The presence of the ancient peptide alpha-melanocyte-stimulating hormone (alpha-MSH) in barrier organs such as gut and skin suggests that this potent anti-inflammatory molecule may be a component of the innate host defense. In tests of antimicrobial activities, alpha-MSH and its fragment KPV showed inhibitory influences against the gram-positive bacterium Staphylococcus aureus and the yeast Candida albicans. Anti-tumor necrosis factor and antimicrobial effects of alpha-MSH suggest that the peptide might likewise reduce replication of ***human*** ***immunodeficiency*** ***virus*** (***HIV***). Treatment with alpha-MSH reduced ***HIV*** replication in chronically and acutely infected human monocytes. At the molecular level, alpha-MSH inhibited activation of the transcription factor NF-kappa B known to enhance ***HIV*** expression. alpha-MSH that combines antipyretic, anti-inflammatory, and antimicrobial effects could be useful in the treatment of disorders in which infection and inflammation coexist.

L43 ANSWER 3 OF 3 MEDLINE
2000134045 Document Number: 20134045. PubMed ID: 10670585. ***Antimicrobial*** effects of alpha-MSH peptides. Cutuli M; Cristiani S; Lipton J M; ***Catania A*** . (3rd Division of Internal Medicine, IRCCS Ospedale Maggiore, Milano, Italy.) JOURNAL OF LEUKOCYTE BIOLOGY, (2000 Feb) 67 (2) 233-9. Journal code: IWY; 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB The presence of the ancient anti-inflammatory peptide alpha-melanocyte-stimulating hormone [alpha-MSH (1-13), SYSMEHFRWGKPV] in barrier organs such as gut and skin suggests a role in the nonspecific (innate) host defense. alpha-MSH and and its carboxy-terminal tripeptide (11-13, KPV) were determined to have ***antimicrobial*** influences against two major and representative pathogens: Staphylococcus aureus and Candida albicans. alpha-MSH peptides significantly inhibited S. aureus colony formation and reversed the enhancing effect of urokinase on colony formation. ***Antimicrobial*** effects occurred over a broad range of concentrations including the physiological (picomolar) range. Small concentrations of alpha-MSH peptides likewise reduced viability and germ tube formation of the yeast C. albicans. ***Antimicrobial*** influences of alpha-MSH peptides could be mediated by their capacity to increase cellular cAMP. Indeed, this messenger was significantly augmented in peptide-treated yeast and the potent adenylyl cyclase inhibitor dideoxyadenosine (ddAdo) partly reversed the killing activity of alpha-MSH peptides. Reduced killing of pathogens is a detrimental consequence of therapy with anti-inflammatory drugs. Because alpha-MSH has potent anti-inflammatory effects we determined influences of alpha-MSH on C. albicans and S. aureus killing by human neutrophils. alpha-MSH peptides did not reduce killing but rather enhanced it, likely as a consequence of the direct ***antimicrobial*** activity. alpha-MSH peptides that combine antipyretic, anti-inflammatory, and ***antimicrobial*** effects could be useful in treatment of disorders in which infection and inflammation coexist.

L43 ANSWER 2 OF 3 MEDLINE

2001166842 Document Number: 21166411. PubMed ID: 11268348. The neuropeptide alpha-MSH in host defense. ***Catania A*** ; Cutuli M; Garofalo L; Carlin A; Airaghi L; Barcellini W; Lipton J M. (Division of Internal Medicine, Ospedale Maggiore di Milano IRCCS, Via F. Sforza 35, 20122 Milano, Italy.. Anna.Catania@unimi.it) . ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2000) 917 227-31. Ref: 28. Journal code: 5NM; 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB The presence of the ancient peptide alpha-melanocyte-stimulating hormone (alpha-MSH) in barrier organs such as gut and skin suggests that this potent anti-inflammatory molecule may be a component of the innate host defense. In tests of ***antimicrobial*** activities, alpha-MSH and its fragment KPV showed inhibitory influences against the gram-positive bacterium Staphylococcus aureus and the yeast Candida albicans. Anti-tumor necrosis factor and ***antimicrobial*** effects of alpha-MSH suggest that the peptide might likewise reduce replication of human immunodeficiency virus (HIV). Treatment with alpha-MSH reduced HIV replication in chronically and acutely infected human monocytes. At the molecular level, alpha-MSH inhibited activation of the transcription factor NF-kappa B known to enhance HIV expression. alpha-MSH that combines antipyretic, anti-inflammatory, and ***antimicrobial*** effects could be useful in the treatment of disorders in which infection and inflammation coexist.

L43 ANSWER 1 OF 3 MEDLINE
2001173590 Document Number: 21120505. PubMed ID: 10996524. Alpha-melanocyte-stimulating hormone in normal human physiology and disease states. ***Catania A*** ; Airaghi L; Colombo G; Lipton J M. (Third Division of Internal Medicine, Padiglione Granelli, Ospedale Maggiore di Milano IRCCS, Via F. Sforza 35, 20122 Milan, Italy.. anna.catania@unimi.it) . TRENDS IN ENDOCRINOLOGY AND METABOLISM, (2000 Oct) 11 (8) 304-8. Ref: 59. Journal code: DX8; 9001516. ISSN: 1043-2760. Pub. country: United States. Language: English.

AB Over the past two decades, research in animal models has indicated that alpha-melanocyte-stimulating hormone (alpha-MSH) has potent anti-inflammatory properties. Furthermore, recent data show that the peptide has ***antimicrobial*** effects and probably contributes to innate immunity. alpha-MSH, which is produced by many extrapituitary human cells, should no longer be considered solely a pituitary hormone; rather, it should be viewed as a ubiquitous modulatory peptide.

L56 ANSWER 8 OF 9 MEDLINE
92396649 Document Number: 92396649. PubMed ID: 1523192. Recent developments in peptide drug delivery to the brain. Pardridge W M. (Department of Medicine, UCLA School of Medicine 90024.) PHARMACOLOGY AND TOXICOLOGY, (1992 Jul) 71 (1) 3-10. Ref: 52. Journal code: PHT; 8702180. ISSN: 0901-9928. Pub. country: Denmark. Language: English.

AB ***Peptide*** - ***based*** ***therapeutics*** are highly water-soluble compounds that do not readily enter brain from blood owing to poor transport through the brain capillary endothelial wall, i.e., the blood-brain barrier (BBB). Strategies available for peptide drug delivery to brain include: (a) neurosurgical-based (intraventricular drug infusion, hyperosmotic opening of the BBB); (b) pharmacological-based (peptide lipidization, liposomes); and (c) physiological-based (biochemical opening of the BBB, chimeric peptides). Chimeric peptides are formed by the covalent coupling of a pharmaceutical peptide (that is normally not transported through the BBB) to a brain transport vector that undergoes absorptive-mediated or receptor-mediated transcytosis through the BBB. The most efficient brain transport vector known to date is a monoclonal

antibody to the transferrin receptor, and this vector achieves a brain volume of distribution approximately 18-fold greater than the plasma space by 5 hr after a single intravenous injection of antibody. The chimeric peptides are formed generally with chemical-based linkers. However, avidin/biotin-based linkers allow for high yield coupling of drug to vector, and for the release of biologically-active peptide following cleavage of the chimeric peptide linker. These strategies may also be used for the delivery of antisense oligonucleotide-based therapeutics to brain. In conclusion, the development of efficacious neuropharmaceuticals in the future will require the development of both drug delivery and drug discovery strategies that operate in parallel.

L58 ANSWER 20 OF 27 MEDLINE
96000403 Document Number: 96000403. PubMed ID: 7578352. Biodegradable polymers for protein and ***peptide*** ***drug*** ***delivery*** . Gombotz W R; Pettit D K. (Department of Drug Delivery and Formulation, Immunex Corporation, Seattle, Washington 98101, USA.) BIOCONJUGATE CHEMISTRY, (1995 Jul-Aug) 6 (4) 332-51. Ref: 234. Journal code: A1T; 9010319. ISSN: 1043-1802. Pub. country: United States. Language: English.

AB We have reviewed a large cross-section of degradable polymeric delivery systems for protein and peptide pharmaceuticals. These systems include monolithic type devices in which the drug is dispersed throughout the polymer and protein-polymer conjugates where the drug is covalently bound to the polymer. These delivery systems have unique challenges associated with their development that are related to both protein stability and protein release kinetics. Despite numerous reports in the scientific literature which include many encouraging results in preclinical models, very few of these systems have been developed into viable products. The products that have made it to market, however, have proven to be very successful and demonstrate the significant advantages that these systems can provide. The continuous advances in biotechnology will produce more proteins and peptides that will be difficult to administer by conventional means, and an increased demand for controlled or site-specific delivery systems is anticipated.

L58 ANSWER 26 OF 27 MEDLINE
92102662 Document Number: 92102662. PubMed ID: 1367763. The anatomy of access: ***peptide*** ***drug*** ***delivery*** . Edgington S M. BIO/TECHNOLOGY, (1991 Dec) 9 (12) 1326-31. Journal code: AL1; 8309273. ISSN: 0733-222X. Pub. country: United States. Language: English.

L58 ANSWER 25 OF 27 MEDLINE
93028125 Document Number: 93028125. PubMed ID: 1409387. Structural specificity of mucosal-cell transport and metabolism of peptide drugs: implication for oral ***peptide*** ***drug*** ***delivery*** . Bai J P; Amidon G L. (University of Minnesota, College of Pharmacy, Minneapolis 55455.) PHARMACEUTICAL RESEARCH, (1992 Aug) 9 (8) 969-78. Ref: 84. Journal code: PHS; 8406521. ISSN: 0724-8741. Pub. country: United States. Language: English.

AB The brush border membrane of intestinal mucosal cells contains a peptide carrier system with rather broad substrate specificity and various endo- and exopeptidase activities. Small peptide (di-/tripeptide)-type drugs with or without an N-terminal alpha-amino group, including beta-lactam antibiotics and angiotensin-converting enzyme (ACE) inhibitors, are transported by the peptide transporter. Polypeptide drugs are hydrolyzed by brush border membrane proteolytic enzymes to di-/tripeptides and amino acids. Therefore, while the intestinal brush border membrane has a carrier system facilitating the absorption of di-/tripeptide drugs, it is a major

barrier limiting oral availability of polypeptide drugs. In this paper, the specificity of peptide transport and metabolism in the intestinal brush border membrane is reviewed.

L54 ANSWER 1 OF 2 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-664959 [64] WPIDS
CR 2000-628219 [60]
DNC C2000-201417
TI Antimicrobial agents derived from alpha-melanocyte stimulating hormone useful for reducing germination of yeast and treating inflammation in human and veterinary disorders.
DC B04
IN ***CATANIA, A P*** ; LIPTON, J M
PA (ZENG-N) ZENGEN INC
CYC 80
PI WO 2000059527 A1 20001012 (200064)* EN 44p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 2000036293 A 20001023 (200107)
ADT WO 2000059527 A1 WO 2000-US6917 20000317; AU 2000036293 A AU 2000-36293 20000317
FDT AU 2000036293 A Based on WO 200059527
PRAI US 1999-126233 19990324

AB WO 200059527 A UPAB: 20010202
NOVELTY - An antimicrobial agent including amino acid sequences derived from alpha-melanocyte stimulating hormone (alpha -MSH) selected from one or more peptides including a specific amino acid sequence, is new.

DETAILED DESCRIPTION - An antimicrobial agent including amino acid sequences derived from alpha-melanocyte stimulating hormone (alpha -MSH) selected from one or more peptides including a specific amino acid sequence, is new. The amino acid sequence is LysProVal, or MetGluHisPheArgTrpGly or their biologically functional equivalent, is new.

ACTIVITY - Antiinflammatory; antibacterial; antifungal.

MECHANISM OF ACTION - Inhibitor of cell growth. Staphylococcus aureus was incubated in the presence or absence of SerTyrSerMetGluHisPheArgTrpGly LysProVal or the LysProVal dimer at concentrations in the range of 10-15-10-4 M for 2 hours at 37 deg. C. Cells were then washed in distilled water and diluted with Hank's balanced salt solution (HBSS). Aliquots were dispensed on blood agar plates and incubated for 24 hours at 37 deg. C. Organism viability was estimated from the number of colonies formed. The results showed that the peptides inhibited Staphylococcus aureus colony formation. The inhibitory effect occurred over a wide range of concentrations and was significant (p less than 0.01) with peptide concentrations of 10-12-10-4 M.

USE - (I) is useful for reducing the viability of microbes, the germination of yeast and for killing microbes without reducing the killing of microbes by human neutrophils. (I) is also useful for treating inflammation in which there is microbial infection without reducing microbial killing and for increasing the accumulation of cAMP in microbes. The antimicrobial agent is effective against microbes including Staphylococcus aureus or Candida albicans (claimed). The antimicrobial agent is useful as a broad prophylactic against microbial infection and in the treatment of human and veterinary disorders resulting from microbial invasion.

ADVANTAGE - The agent is less toxic and is effective in animals and humans without adverse effects.
Dwg.0/8

L54 ANSWER 2 OF 2 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-628219 [60] WPIDS

CR 2000-664835 [53]
DNC C2000-188213
TI Treating uro-genital conditions, such as vaginitis, cystitis, urethritis, or balanoposthitis comprises using alpha-melanocyte stimulating hormone or a derivative of it .
DC B04 C03
IN ***CATANIA, A*** ; LIPTON, J
PA (ZENG-N) ZENGEN INC
CYC 92
PI WO 2000056353 A2 20000928 (200060)* EN 37p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000037725 A 20001009 (200103)
ADT WO 2000056353 A2 WO 2000-US7846 20000323; AU 2000037725 A AU 2000-37725 20000323
FDT AU 2000037725 A Based on WO 200056353
PRAI US 1999-126233 19990324

AB WO 200056353 A UPAB: 20001214
NOVELTY - A uro-genital condition treatment system comprising a carrier and a polypeptide with a sequence of 3 (I), 7 (II), 8 (III), 13 (IV) amino acids, given in the specification, and/or a biologically functional equivalent (E), is new.

DETAILED DESCRIPTION - A new uro-genital condition treatment system comprises a carrier and a polypeptide with a sequence of 3 (I), 7 (II), 8 (III), 13 (IV) amino acids, given in the specification, and/or (E). (IV) is alpha -melanocyte stimulating hormone (alpha -MSH).

Lys Pro Val (I)

Met Glu His Phe Arg Trp Gly (II)

His Phe Arg Trp Gly Lys Pro Val (III)

Ser Tyr Ser Met Glu His Phe Arg Trp Gly Lys Pro Val (IV)

INDEPENDENT CLAIMS are also included for the following:

(1) a tampon comprising an absorbent material associated with a polypeptide including (I), (II), (III), (IV) and/or (E);

(2) a contraceptive comprising a barrier associated with a carrier that carries a polypeptide including (I), (II), (III), (IV) and/or (E);

(3) a suppository comprising a carrier and a polypeptide including (I), (II), (III), (IV) and/or (E);

(4) treating (A) a uro-genital condition using a polypeptide comprising (I), (II), (III), (IV) and/or (E);

(5) preventing (B) toxic shock syndrome using a polypeptide including (I), (II), (III), (IV) or (E);

(6) preventing (C) infection from sexually transmitted diseases comprising using a contraceptive together with a polypeptide including (I), (II), (III), (IV) and/or (E); and

(7) treating an antibiotic resistant microorganism using a polypeptide including (I), (II), (III), (IV) or (E).

ACTIVITY - Antibacterial; fungicide, virucide; antiinflammatory. Cultures of Staphylococcus aureus (American Type Culture Collection 29213) were incubated in the presence of 10-15 to 10-4 M of (I), (IV) or a dimer of (I) for 2 hours at 37 deg. C. The cells were diluted to a concentration of 100 organisms/ml in Hank's balanced salt solution (HBSS). 1 ml aliquots were dispensed on blood agar plates and incubated for 24 hours at 37 deg. C. Viability of microorganisms was estimated form the colonies formed. (I), (IV) and the dimer of (I) all inhibited S. aureus colony formation. The colony forming units (CFU) of S. aureus at a concentration of 10-12 M of peptides were approximately 100, 40, 30, and

28 % for the control, (IV), (I) and dimer of (I), respectively.

MECHANISM OF ACTION - cAMP stimulator; NF(necrosis factor)-kB inhibitor. Candida albicans (106/ml) was incubated at 37 deg. C with continuous shaking in the presence or absence of 10-6 (IV), (I) or forskolin (an agent known to increase cAMP). cAMP levels were measured using an enzyme immunoassay kit. (IV) and (I) enhanced cAMP content in C. albicans in the same order of magnitude as that induced by equimolar forskolin. The concentration of cAMP was approximately 30, 40, 45, and 65 pmol/ml for equimolar concentrations of a control, (IV), (I), and forskolin, respectively. The results indicate that the polypeptide inhibits growth of C. albicans by increasing cAMP levels, therefore inhibiting mRNA and protein synthesis.

USE - The treatment system is used to treat a uro-genital condition such as vaginitis, cystitis, urethritis, or balanoposthitis, prevent toxic shock syndrome, prevent infection from sexually transmitted diseases and treat an antibiotic resistant microorganism (all claimed). The polypeptide can reduce the viability of microbes, reduce the germination of yeast, kill microbes, treat inflammation associated with microbial infection, increase the accumulation of cAMP in microbes and inhibit replication and expression of viral pathogens.

ADVANTAGE - The polypeptide used in the system has potent antipyretic and antiinflammatory properties, but has extremely low toxicity. It can kill microbes without reducing the killing of microbes by human neutrophils, treat inflammation associated with microbial infection without reducing microbial killing.

L19 ANSWER 12 OF 29 USPATFULL
2001:44199 Pharmaceutical composition containing IFN-.gamma. inducing polypeptide or factor for treating and/or preventing IFN-.gamma. susceptive diseases.
Torigoe, Kakuji, Okayama, Japan
Tanimoto, Tadao, Okayama, Japan
Fukuda, Shigeharu, Okayama, Japan
Kurimoto, Masashi, Okayama, Japan
Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Okayama, Japan (non-U.S. corporation)
US 6207641 B1 20010327
APPLICATION: US 1997-974469 19971120 (8)
PRIORITY: JP 1995-78357 19950310
JP 1995-274988 19950929
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An agent for susceptive diseases, which contains a polypeptide that has a molecular weight of 18,500.+-.3,000 daltons on SDS-PAGE and a pI of 4.9.+-.1.0 on chromatofocusing, strongly induces the IFN-.gamma. production by immunocompetent cells with only a small amount, and does not cause serious side effects even when administered to human at a relatively-high dose. The agent treats and/or prevents malignant tumors, viral diseases, bacterial infectious diseases, and immune diseases including atopies.

CLM What is claimed is:

1. A pharmaceutical composition for inducing human IFN-.gamma., enhancing cytotoxicity of human killer cells or inducing formation of human killer cells, comprising a pharmaceutically acceptable carrier, and as an effective ingredient, 0.000001 w/w % to 100 w/w % on a dry solid basis of a polypeptide of SEQ ID NO:1, where amino acid residue 73 of SEQ ID NO:1, as represented by Xaa, is Ile or Thr, or a homologous polypeptide thereof, wherein the polypeptide and the homologous polypeptide thereof has the following physicochemical properties: (a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, where amino acid residue 73, as represented by Xaa, is Ile or Thr, and a homologous sequence thereof where one amino acid residue in SEQ ID NO:1 is replaced with a different amino acid, or one amino acid residue is added to or deleted from the N-terminus or the C-terminus of SEQ ID NO:1, wherein said homologous polypeptide has substantially the same physicochemical properties and biological activity as the polypeptide of SEQ ID NO:1; (b) Molecular weight 18,500.+-.3,000 daltons on sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE); (c) Isoelectric point (pI) 4.9.+-.1.0 on chromatofocusing; (d) Biological activity Inducing IFN-.gamma. production by human immunocompetent cells; and (d) Acute toxicity Having an LD.sub.50 of at least about one mg/kg when tested in mice.

2. The pharmaceutical composition according to claim 1, wherein said effective ingredient is the polypeptide of SEQ ID NO:1, where amino acid residue 73, as represented by Xaa, is Ile or Thr.

3. The pharmaceutical composition according to claim 2, further comprising at least one member selected from the group consisting of stabilizer, adjuvants, excipients, diluents, and biologically-active substances.

4. The pharmaceutical composition according to claim 3, wherein said stabilizer is at least one member selected from the group consisting of serum albumin, gelatin, maltose, and trehalose.

5. The pharmaceutical composition according to claim 3, wherein said biologically-active substance is at least one member selected form the group consisting of interleukins, interferons, tumor necrosis factors, and antitumor agents.

6. The pharmaceutical composition according to claim 1, wherein said effective ingredient is the homologous polypeptide.

7. The pharmaceutical composition according to claim 6, further comprising at least one member selected from the group consisting of interleukin 2 and concanavalin A.

8. The pharmaceutical composition according to claim 1, wherein the killer cells are selected from the group consisting of natural killer cells, lymphokine-activating killer cells, and cytotoxic T-cells.

9. The pharmaceutical composition according to claim 6, further comprising a stabilizer selected from the group consisting of serum albumin, gelatin, maltose, and trehalose.

TI Pharmaceutical composition containing IFN-.gamma. inducing polypeptide or factor for treating and/or preventing IFN-.gamma. susceptive diseases

AB An agent for susceptive diseases, which contains a polypeptide that has a molecular weight of 18,500.+-.3,000 daltons on SDS-PAGE and a pI of 4.9.+-.1.0 on chromatofocusing, strongly induces the. . .

SUMM The present invention relates to an agent for susceptive diseases which contains as an effective ingredient a novel polypeptide that induces the interferon-.gamma. (hereinafter abbreviated as "IFN-.gamma.") production by immunocompetent cells.

SUMM . . . object of the present invention is attained by an agent for susceptive diseases which contains as an effective ingredient a polypeptide having either the amino acid sequence of SEQ ID NO:1 (where the symbol "Xaa" represents "isoleucine" or "threonine") or its. . .

SUMM The present invention was made based on the finding of a novel polypeptide which induces the IFN-.gamma. production by immunocompetent cells. The present inventors studied cytokines produced from mammalian cells and have found. . .

SUMM . . . which encodes another novel substance that induces the IFN-.gamma. production by immunocompetent cells. They revealed that the substance is a polypeptide, and they decoded its DNA, and found that the polypeptide has the amino acid sequence of SEQ ID NO:1. They introduced the DNA into Escherichia coli to express the polypeptide and to obtain the polypeptide in the resultant culture in a considerably high yield. These findings were disclosed in Japanese Patent Application Nos.184,162/94 and 304,203/94, filed by the present applicant. The present invention provides uses of the polypeptide as an agent for susceptive disease.

DRWD KGFHH2 cDNA: cDNA encoding the present polypeptide

DETD . . . immunocompetent cells, and exerts a therapeutic and/or prophylactic effect on patients suffering from IFN-.gamma. susceptive

diseases when administered. When a polypeptide has an activity of enhancing the cytotoxicity of killer cells or of inducing the formation of killer cells, it exerts. . .

DETD The polypeptide used in the present invention has either the amino acid sequence of SEQ ID NO:1 (where the symbol "Xaa" represents. . . polypeptides such as, those isolated from natural sources by cell culture and those artificially synthesized by recombinant DNA technology and peptide synthesis, can be used in the present invention as long as they have either of these amino acid sequences and. . .

DETD . . . a conventional manner, and the resulting cultures are purified by conventional techniques used for purifying cytokines to obtain the objective polypeptide. Japanese Patent Application No.304,203/94, filed by the present applicant, discloses in detail the preparation of the polypeptide using recombinant DNA technology, and Japanese Patent Application No.58240/95, titled "Monoclonal antibody", filed by the present applicant on Feb. 23, 1995, discloses a purification method which can produce a polypeptide with the highest possible purity at the lowest possible labor- and material-costs.

DETD As described above, the polypeptide has a property of inducing the IFN-.gamma. production by immunocompetent cells. When administered to human, the present agent for susceptive. . . IFN-.gamma. production by immunocompetent cells in vivo, and exerts a satisfactory therapeutic and/or prophylactic effect on IFN-.gamma. susceptive diseases. The polypeptide having the amino acid sequence of SEQ ID NO:1 has the properties of enhancing the cytotoxicity of killer cells such. . . as the property of inducing the IFN-.gamma. production by immunocompetent cells, so that the killer cells treat and/or prevent the polypeptide-susceptive diseases. Thus, the wording "susceptive diseases" as referred to in the present specification means diseases in general which include IFN-.gamma.. . . adult T cell leukemia, chronic myelogenous leukemia, and malignant leukemia; and immune diseases such as allergy and rheumatism. When the polypeptide is used along with interleukin 3, it exerts a strong effect on the treatment or the remission of leukemia and. . .

DETD . . . present agent is generally processed into an agent in the form of a liquid, paste or solid which contains the polypeptide in an amount of 0.000001-100 w/w %, preferably, 0.0001-0.1 w/w %, on a dry solid basis (d.s.b.).

DETD The present agent can be used intact or processed into compositions by mixing with a physiologically-acceptable carrier, adjuvant, excipient, diluent, and/or stabilizer, and, if necessary, further mixing with one or more other biologically-active substances such as interferon-.alpha.,. . . vincristine, vinblastine, L-asparaginase, radio gold colloidal, KRESTIN.RTM., picibanil, lentinan, and Maruyama vaccine. Among these combinations, a composition consisting of the polypeptide and interleukin 2 is especially useful because interleukin 2 acts as a cofactor for the polypeptide when inducing the IFN-.gamma. production by immunocompetent cells. The combination of the polypeptide and a natural or recombinant human interleukin 2 induces a prescribed level of IFN-.gamma. production even when the sole use of the polypeptide could not substantially induce the IFN-.gamma. production by immunocompetent cells. The use of a combination of the polypeptide and interleukin 12 induces a greater level of IFN-.gamma. production that could not be readily attained by their respective use. Because the polypeptide increases the inhibitory activity of interleukin 12 on the production of immunoglobulin E antibody, the polypeptide can be used as an agent to treat atopies including allergic asthma,

atopic bronchial asthma, hay fever, allergic rhinitis, atopic dermatitis, vascular edema, and atopic disorder of the digestive system. The sole administration of the polypeptide attains a desired therapeutic effect on humans because there inherently exists interleukin 12 in the human body, though the amount. . .

DETD . . . includes those in a unit dose form meaning a physically separated and formed medicament suitable for administration, and contains the polypeptide in a daily dose or in a dose from 1/40 to several folds (up to 4 folds) of the daily. . .

DETD The agent for susceptive diseases can be orally or parenterally administered to patients, and as described below it can be used to activate antitumor cells in vitro. In both administrations,. . . varies depending on the types of susceptive diseases and their symptoms, the agent can be orally administered to patients or parenterally administered to patients' intradermal tissues, subcutaneous tissues, muscles, and veins at a dose in the range of about 0.1-50 mg/shot,. . .

DETD . . . activated in vitro by interleukin 2 (adoptive immunotherapy). The immunotherapeutic effect can be significantly enhanced when administered along with the polypeptide. In method (i), the polypeptide is administered to patients in an amount of about 0.1 .mu.g/shot/adult to one mg/shot/adult at 1-10 times simultaneously or before. . . of about 10,000 to 1,000,000 units/shot/adult, though it varies depending on the types of malignant tumors, patients' symptoms, and the polypeptide dose. While in method (ii), mononuclear cells and lymphocytes, collected from patients with malignant tumors, are cultured in the presence of interleukin 2 and about one ng to one mg of the polypeptide per 1.times.10.sup.6 cells of these blood cells. After culturing for a prescribed period of time, NK cells and LAK cells. . .

DETD The following Experiments explain the preparation of the polypeptide by recombinant DNA technology, and the biological activity and toxicity:

DETD Preparation of Polypeptide

DETD . . . prepared from a phage DNA clone by the method in Japanese Patent Application No.304,203/94 and containing a DNA encoding the polypeptide of SEQ ID NO:1, and an adequate amount of a sense primer and an antisense primer represented by 5'-ATAGAATTCAAATGTACTTTGGCAAGCTTGAATC-3' (SEQ. . .

DETD . . . Eco RI and Hind III at the 5'- and 3'-terminals of SEQ ID NO:2, a methionine codon which initiates the polypeptide synthesis and positions in the sites corresponding to those before and after the N- and C-termini of SEQ ID NO:2, and a TAG codon which terminates the polypeptide synthesis.

DETD Production and Purification of Polypeptide from Transformant KGFHH2

DETD . . . gel for immunoaffinity chromatography was prepared and packed in a plastic cylindrical column which was then washed with phosphate buffered saline (hereinafter abbreviated as "PBS"), fed with 10 ml of the fractions eluted from the PHENYL SEPHAROSE column at about 1.0. . . resultant concentrate for IFN-.gamma. inducibility and protein content, which revealed that the purification procedure yielded about 25 mg of the polypeptide with a purity at least 95% per one L of culture.

DETD Analysis according to the method in Japanese Patent Application No. 304,203/94 revealed that the purified polypeptide had the following physicochemical properties: When electrophoresed in SDS-polyacrylamide gel under reducing conditions, the purified protein appeared as a main. . .

DETD A polypeptide obtained by the method in Experiment 1-2 was diluted to give an appropriate concentration with RPMI 1640 medium (pH 7.4). . . well was sampled and assayed for IFN-.gamma. content with conventional enzyme immunoassay. As a control, a system free of the polypeptide was provided, and similarly treated as above. The results are presented in Table 1. In the Table, the IFN-.gamma. content. . .

DETD TABLE 1

IFN-.gamma. productivity (IU/ml)

Polypeptide concentration (ng/ml)	Polypeptide	Polypeptide plus 0.5 .mu.g/ml of concanavalin A	Polypeptide plus 10 U/ml of interleukin 2
0	0	0	0
1.6	1 .+-. 2	92 .+-. 32	184 .+-. 12
8.0	3 .+-. 1	220. . .	

DETD The results in Table 1 show that lymphocytes as immunocompetent cells produced IFN-.gamma. when the polypeptide acts on them. As is evident from the results, the combination use of the polypeptide and interleukin 2 or concanavalin A as a cofactor enhanced IFN-.gamma. production.

DETD . . . cell density of 1.times.10.sup.6 cells/ml, and the suspension was distributed into 12-well microplates in an amount of 0.5 ml/well. A polypeptide obtained by the method in Experiment 1-2 was appropriately diluted with a fresh preparation of the same medium, and the. . .

DETD TABLE 2

Concentration of polypeptide (pM*)	Concentration of interleukin 2 (unit/ml)	Cytotoxicity (%) (Effector cell): (Target cell) 2.5:1	5:1	10:1
0	0	22	35	65
0	10	30	48	73
0.5	0	23	36	66
0.5	10. . .			

DETD The results in Table 2 show that the polypeptide has an activity of enhancing the cytotoxicity by NK cells. As is shown in Table 2, the coexistence of interleukin. . .

DETD TABLE 3

Concentration of polypeptide (pM*)	Concentration of interleukin 2 (unit/ml)	Cytotoxicity (%) (Effector cell): (Target cell) 5:1	10:1	20:1
0	0	11	21	34
0	10	15	28	38
0.5	0	13	22	35
0.5	10. . .			

DETD The results in Table 3 show that the polypeptide has an activity of inducing the formation of LAK cells. As is shown in the results, the coexistence of interleukin. . .

DETD According to what is done conventionally, a purified polypeptide obtained by the method in Experiment 1-2 was percutaneously, perorally or intraperitoneally administered to 8-week-old mice. As a result, the LD.sub.50 of the purified polypeptide was about one mg/kg or higher and independent of the administration routes. This evidences that the polypeptide can be safely incorporated into pharmaceuticals for administering human.

DETD . . . complete treatment or remission. In these circumstances, and as is evident from the results in Experiments 2 and 3, the

polypeptide induces the IFN-.gamma. production by immunocompetent cells, and enhances the cytotoxicity by NK cells or induces the formation of LAK. . .

DETD A polypeptide, obtained by the method in Experiment 1-2, was dissolved in physiological saline containing one w/v % human serum albumin as a stabilizer to obtain a one mg/ml polypeptide solution which was then sterilized by membrane filter to obtain a solution.

DETD A polypeptide, obtained by the method in Experiment 1-2, was dissolved in 100 ml physiological saline containing one w/v % purified gelatin as a stabilizer, and the solution was in the usual manner sterilized with a membrane filter. One ml aliquots of. . .

DETD . . . trehalose were dissolved in distilled water to give concentrations of 1.4 w/w % and 2.0 w/w %, respectively, and a polypeptide obtained by the method in Experiment 1-2 was dissolved to homogeneity in the solution, followed by adjusting the pH of the resultant solution to pH 7.2 to obtain a paste containing about one mg/g of the polypeptide.

DETD A polypeptide, obtained by the method in Experiment 1-2, and LUMIN, i.e. [bis-4-(1-ethylquinoline)][.gamma.-4'-(1-ehtylquinoline] pentamethionine cyanine, as a cell activator were mixed to. . . mixture was in usual manner tabletted by a tabletting machine to obtain tablets, about 200 mg weight each, containing the polypeptide and the LUMIN, about one mg each.

DETD . . . to 37.degree. C. to give a cell density of about 1.times.10.sup.6 cells/ml, and mixed with about 1.0 .mu.g/ml of a polypeptide, obtained by the method in Experiment 1-2, and about 100 units/ml of a recombinant human interleukin 2, followed by incubating. . .

DETD . . . diseases such as malignant tumors, viral diseases, bacterial infectious diseases, and immune diseases. Furthermore, the present agent which contains a polypeptide having an activity of enhancing the cytotoxicity by killer cells or inducing the formation of killer cells exert a significant. . .

1. A pharmaceutical composition for inducing human IFN-.gamma., enhancing cytotoxicity of human killer cells or inducing formation of human killer cells, comprising a pharmaceutically acceptable carrier, and as an effective ingredient, 0.000001 w/w % to 100 w/w % on a dry solid basis of a polypeptide of SEQ ID NO:1, where amino acid residue 73 of SEQ ID NO:1, as represented by Xaa, is Ile or Thr, or a homologous polypeptide thereof, wherein the polypeptide and the homologous polypeptide thereof has the following physicochemical properties: (a) an amino acid sequence selected from the group consisting of SEQ ID NO:1,. . . acid residue is added to or deleted from the N-terminus or the C-terminus of SEQ ID NO:1, wherein said homologous polypeptide has substantially the same physicochemical properties and biological activity as the polypeptide of SEQ ID NO:1; (b) Molecular weight 18,500.+-.3,000 daltons on sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE); (c) Isoelectric point. . .

2. The pharmaceutical composition according to claim 1, wherein said effective ingredient is the polypeptide of SEQ ID NO:1, where amino acid residue 73, as represented by Xaa, is Ile or Thr.

3. The pharmaceutical composition according to claim 2, further comprising at least one member selected from the group consisting of stabilizer, adjuvants, excipients, diluents, and

biologically-active substances.

4. The pharmaceutical composition according to claim 3, wherein said stabilizer is at least one member selected from the group consisting of serum albumin, gelatin, maltose, and trehalose.

5. The pharmaceutical composition according to claim 3, wherein said biologically-active substance is at least one member selected form the group consisting of interleukins,. . .
6. The pharmaceutical composition according to claim 1, wherein said effective ingredient is the homologous polypeptide.

7. The pharmaceutical composition according to claim 6, further comprising at least one member selected from the group consisting of interleukin 2 and concanavalin. . .
8. The pharmaceutical composition according to claim 1, wherein the killer cells are selected from the group consisting of natural killer cells, lymphokine-activating killer. . .
9. The pharmaceutical composition according to claim 6, further comprising a stabilizer selected from the group consisting of serum albumin, gelatin, maltose, and trehalose.

L19 ANSWER 17 OF 29 USPATFULL
2000:74274 Neuropeptide Y analogues, compositions and methods of lowering blood pressure.
Nyce, Jonathan W., Greenville, NC, United States
Leonard, Sherry Ann, Greenville, NC, United States
East Carolina University, Greenville, NC, United States (U.S. corporation)
US 6075009 20000613
APPLICATION: US 1995-422839 19950417 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Neuropeptide Y analogues, and their compositions are effective for lower blood pressure.
CLM What is claimed is:
1. A modified Neuropeptide Y, having blood pressure lowering activity and consisting of a fragment of 8 to 18 amino acids of a Neuropeptide Y, which fragment comprises an amino acid segment selected from the group consisting of amino acids 28 to 35 of a Neuropeptide Y, wherein D-Thr is substituted for Thr at position 32; pharmaceutically acceptable salts thereof; and mixtures thereof.

2. The modified Neuropeptide Y of claim 1, comprising 9 to 17 amino acids.

3. The modified Neuropeptide Y of claim 2, comprising 10 to 16 amino acids.

4. The modified Neuropeptide Y of claim 3, comprising 15 amino acids.

5. The modified Neuropeptide Y of claim 4, which is selected from the group consisting of D-Tyr-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Tyr-NH.sub.2 (SEQ ID NO: 1); D-Tyr-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Tyr-NH.sub.2 (SEQ ID NO: 2); D-Asp-Pro-Lys-Ser-Pro-Tyr-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Tyr-NH.sub.2 (SEQ ID No: 3); Ac-D-Asp-Pro-Lys-Ser-Pro-Tyr-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Tyr-NH2 (SEQ ID No: 4);

D-Phe(NO2)-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Phe(NO2)-NH2 (SEQ ID NO: 5); Ac-D-Phe(NO2)-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Phe(NO2)-NH2 (SEQ ID NO: 6); D-Phe(pF)-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Phe(pF)-NH2 (SEQ ID NO: 7); Ac-D-Phe(pF)-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Phe(pF)-NH2 (SEQ ID NO: 8); D-Phe(pCl)-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Phe(pCl)-NH2 (SEQ ID NO: 9); Ac-D-Phe(pCl)-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Phe(pCl)-NH2 (SEQ ID NO: 10); D-Phg-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Phg-NH2 (SEQ ID NO: 11); and D-Phg-Ile-Asn-Leu-Ile-D-Thr-Arg-Gln-Arg-D-Phg-NH2 (SEQ ID NO: 12); wherein Ac represents acetyl, Phe(NO.sub.2) represents NO.sub.2 substituted phenylalanine, Phe(pCl) represents phenylalanine substituted by Cl on the phenylalanine ring, and Phe(pF) represents phenylalanine substituted by F on the phenylalanine.

6. The modified Neuropeptide Y of claim 5, which is freeze-dried or lyophilized.

7. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 1, a pharmaceutically acceptable salt thereof or mixtures thereof.

8. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 2, a pharmaceutically acceptable salt thereof or mixtures thereof.

9. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 3, a pharmaceutically acceptable salt thereof or mixtures thereof.

10. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 4, a pharmaceutically acceptable salt thereof or mixtures thereof.

11. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 5, a pharmaceutically acceptable salt thereof or mixtures thereof.

12. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 6, a pharmaceutically acceptable salt thereof or mixtures thereof.

13. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 7, a pharmaceutically acceptable salt thereof or mixtures thereof.

14. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 8, a pharmaceutically acceptable salt thereof or mixtures thereof.

15. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 9, a pharmaceutically acceptable salt thereof or mixtures thereof.

16. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 10, a pharmaceutically acceptable salt thereof or mixtures thereof.

17. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 11, a pharmaceutically acceptable salt thereof or mixtures thereof.

18. The modified Neuropeptide Y of claim 5, which is SEQ. ID NO: 12, a pharmaceutically acceptable salt thereof or mixtures thereof.

19. A peptide, comprising the modified Neuropeptide Y of claim 1, and a Neuropeptide Y unrelated amino acid segment, a pharmaceutically acceptable salt thereof or mixtures thereof.

20. A composition, comprising the modified Neuropeptide Y of claim 1, and a carrier.

21. The composition of claim 8, wherein the carrier is a physiologically acceptable carrier.

22. The composition of claim 9, wherein the carrier is a pharmaceutically acceptable carrier.

23. The composition of claim 8, comprising about 0.5 to about 99% of the modified Neuropeptide Y.

24. The composition of claim 8, in unit dosage form.

25. The composition of claim 8, in multi-dosage form.

26. The composition of claim 8, in bulk.

27. The composition of claim 8, wherein the carrier is selected from the group consisting of solid and liquid carriers .

28. The composition of claim 8, further comprising an agent selected from the group consisting of other therapeutic agents, flavorings, lubricants, suspending and thickening agents, binders, inert diluents, surface active agents, dispersants, antioxidants, buffers, bacteriostats and solutes to attain isotonicity.

29. The composition of claim 28, comprising a therapeutic agent is a tubercular agent.

30. A formulation, comprising the composition of claim 8, which is selected from the group consisting of inhalation, oral, rectal, topical, parenteral, and transdermal formulations.

31. The formulation of claim 30, which is selected from the group consisting of buccal, sublingual, dermal, intraocular, subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and transdermal formulations.

32. The formulation of claim 30, in a form selected from the group consisting of capsules, cachets, pastilles, lozanges, powder, granules, solution, suspension, emulsion and tablets.

33. The formulation of claim 32, comprising a suspension or solution in an aqueous or non-aqueous liquid or an oil-in-water or water-in-oil emulsion.

34. The formulation of claim 32, provided in a capsule.

35. The formulation of claim 30, which is a parenteral formulation.

36. The parenteral formulation of claim 35, comprising an injectable formulation.

37. The formulation of claim 30, which is an oral formulation.

38. The oral formulation of claim 37, which is a solution or suspension selected from the group consisting of aqueous and non-aqueous liquid solutions and suspensions.

39. The oral formulation of claim 37, which is an emulsion selected from the group consisting of oil-in-water and water-in-oil emulsions.

40. The oral formulation of claim 30, which is a buccal or sub-lingual formulation selected from the group consisting of lozenges further comprising a flavoring agent selected from the group consisting of sucrose, acacia and tragacanth; and pastilles further comprising an inert base selected from the group consisting of gelatin, glycerin, sucrose and acacia.

41. The oral formulation of claim 30, further comprising an enteric coating.

42. The parenteral formulation of claim 30, comprising a solution, suspension or emulsion.

43. The injectable formulation of claim 36, selected from the group consisting of injectable solutions or suspensions, and which may further comprise an agent selected from the group consisting of antioxidants, buffers, bacteriostatic agents and solutes which render the solution or suspension isotonic with the blood of a recipient.

44. The injectable formulation of claim 43, wherein the solutions and suspensions are selected from the group consisting of sterile aqueous and non-aqueous injection solutions and suspensions, which may further comprise suspending agents and thickening agents.

45. The formulation of claim 38, in unit-dose form.

46. The formulation of claim 30, which is in bulk or multi-dose form.

47. The formulation of claim 35, which is provided in multi-dose or bulk form selected from the group consisting of sealed ampoules and vials, respectively.

48. The formulation of claim 30, which is freeze-dried or lyophilized.

49. The formulation of claim 30, which is a topical formulation selected from the group consisting of ointments, creams, lotions, pastes, gels, sprays, aerosols and oils; and may further comprise a carrier selected from the group consisting of vaseline, lanoline, polyethylene glycols, alcohols and trans-dermal enhancers.

50. The formulation of claim 30, which is a transdermal formulation.

51. The transdermal formulation of claim 50, which is an iontophoretic formulation selected from the group consisting of iontophoretic solutions and suspensions, and which may further comprise a buffer.

52. A sub-lingual formulation comprising the composition of claim 30, wherein the flavoring and inert diluent are selected from the group consisting of sucrose, acacia, tragacanth, gelatin and glycerin.

53. An ampoule or vial comprising the formulation of claim 30.

54. A rectal formulation comprising the composition of claim 30, in unit

dosage form.

55. A transdermal formulation comprising the composition of claim 30, and an iontophoretic medium.

56. A transdermal device, comprising a patch which comprises the formulation of claim 55.

57. An iontophoretic device comprising the transdermal device of claim 56, and means for iontophoretic delivery.

58. A method of lowering blood pressure, comprising administering to a subject in need of such treatment a blood pressure lowering amount of the modified Neuropeptide Y of claim 1.

59. The method of claim 58, wherein the agent is administered as a composition further comprising a pharmaceutically acceptable carrier.

60. The method of claim 58, which is a prophylactic method.

61. The method of claim 58, which is a therapeutic method.

62. The method of claim 58, wherein the agent is administered parenterally.

63. The method of claim 58, wherein the agent is administered orally.

64. The method of claim 58, wherein the agent is administered transdermally.

65. The method of claim 58, wherein the agent is administered in an amount of about 400 to about 4000 nmole/kg body weight.

66. The method of claim 58, wherein the subject is human.

67. The method of claim 58, wherein the subject is an animal.

68. A method of treating a disease or condition associated with high blood pressure, comprising administering to a subject in need of such treatment the method of claim 48, wherein the modified Neuropeptide Y is administered in an anti-disease or condition effective amount.

69. The method of claim 58, wherein the agent is administered anally.

70. The method of claim 58, wherein the agent is administered transdermally.

71. The method of claim 58, wherein the modified Neuropeptide Y is administered by inhalation.

72. The method of claim 58, wherein the modified Neuropeptide Y is administered intraocularly.

73. The method of claim 58, wherein the modified Neuropeptide Y is administered sublingually.

74. The method of claim 58, wherein the modified Neuropeptide Y is administered buccally.

75. The method of claim 58, wherein the modified Neuropeptide Y is administered by a route selected from the group consisting of subcutaneous, intradermal, intramuscular, intravenous and intraarticular.

76. The method of claim 58, wherein the modified Neuropeptide Y is administered dermally.

77. The method of claim 76, wherein the modified Neuropeptide Y is administered by means of a patch.

78. The method of claim 58, wherein the modified Neuropeptide Y is administered by iontophoresis.

79. The modified Neuropeptide Y of claim 5, which is selected from the group consisting of SEQ. ID NO: 3 and SEQ. ID NO: 4, pharmaceutically acceptable salt thereof and mixtures thereof.

SUMM Neuropeptide Y is a 36 amino acid member of the pancreated polypeptide family. It is highly concentrated in both the central and peripheral mammalian nervous system. It apparently serves important functions in. . .

SUMM The present invention relates to a pharmaceutical formulation comprising the active compounds given above in combination with a pharmaceutically acceptable carrier. The active compound maybe included in the formulation in a pharmaceutically effective amount i.e., an amount effective to lower blood. . .

SUMM Pharmaceutical compositions for use in the present method of lowering blood pressure include those suitable for inhalation, oral, rectal, topical, (including buccal, sublingual, dermal and intraocular) parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular) and transdermal administration. The compositions may conveniently be presented in unit dosage form. . .

SUMM . . . active agents or the physiologically acceptable salts thereof (the "active compound") are typically admixed with, among other things, an acceptable carrier. The carrier must be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation,. . .

SUMM . . . by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or. . .

SUMM . . . a flavored base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

SUMM Formulations of the present invention suitable for parenteral administration comprise sterile aqueous and non-aqueous injection solutions of the active compound, which preparations are preferably isotonic with the blood. . . ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or

water-for-injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets. . .

SUMM . . . presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

SUMM Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

DETD NPY27-36 (D-Tyr.sup.27,36, D-Thr.sup.32) was synthesized using Fmoc-BOP chemistry in accordance with known techniques. The automated BIOSEARCH model 9600 peptide synthesizer was used to produce the peptide. The amino acid derivatives were Arg (Mtr), Ile, Leu, Thr (tBu), tYR (tBu), Asn (Tmob) and Gln (Tmob). Tyr.sup.27, Thr.sup.32. . . from the resin (PAL resin), TFA/thioanisol/ethanedithiol/anisol was used in molar excess (10 ml/g). After deprotection of the final product, the peptide was purified over a 2".times.25 cm VYDAC 15-20 micron C.sub.18 column using a Waters model 600-E HPLC with 0.1% TFA. . .

DETD . . . and diastolic pressures and heart rate from the femoral artery catheter. Patency of catheters was verified by flushing with either saline or 10% heparin.

DETD . . . or 1000 nM/kg (nanomoles per liter per kilogram) of NPY27-36 (D-Tyr.sup.27,36, D-Thr.sup.32) (prepared as described in Example 1 above), or saline was delivered to the animal via the catheter in the left femoral vein. Changes in systolic and diastolic pressures and. . .

DETD . . . to the normotensive Sprague-Dawsley rats. Doses of 30 and 100 nM/kg failed to produce changes that were significantly different from saline treatment. When given in doses of 500, 800, and 1000 nM/Kg, however, significantly different decreases in mean arterial pressure were seen as compared to saline-treated controls. Further, doses of 500 and 1000 nM/kg produced significantly different increases in heart rate as compared to saline controls.

DETD . . . (i) SEQUENCE CHARACTERISTICS:
#acids (A) LENGTH: 10 amino
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (ix) FEATURE:
(A) NAME/KEY: Modified-sit - #e
(B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#D /label=
#"D isomer of tyrosine"
- (ix) FEATURE:
(A) NAME/KEY:. . . (i) SEQUENCE CHARACTERISTICS:
#acids (A) LENGTH: 10 amino
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (ix) FEATURE:
(A) NAME/KEY: Modified-sit - #e
(B) LOCATION: 1

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#/product= "OTHER"R INFORMATION:
#D              /label=
#"D isomer of tyrosine"
-      (ix) FEATURE:
            (A) NAME/KEY:.  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids      (A) LENGTH: 15 amino
            (B) TYPE: amino acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear
-      (ii) MOLECULE TYPE: peptide
-      (ix) FEATURE:
            (A) NAME/KEY: Modified-sit - #e
            (B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#D              /label=
#"D isomer of aspartic acid"
-      (ix) FEATURE:
            (A).  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids      (A) LENGTH: 15 amino
            (B) TYPE: amino acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear
-      (ii) MOLECULE TYPE: peptide
-      (ix) FEATURE:
            (A) NAME/KEY: Modified-sit - #e
            (B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#D              /label=
#"D isomer of aspartic acid"
-      (ix) FEATURE:
            (A).  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids      (A) LENGTH: 10 amino
            (B) TYPE: amino acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear
-      (ii) MOLECULE TYPE: peptide
-      (ix) FEATURE:
            (A) NAME/KEY: Modified-sit - #e
            (B) LOCATION: 1
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#D              /label=
#"D isomer of phenylalanine"
-      (ix) FEATURE:
            (A) NAME/KEY:.  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids      (A) LENGTH: 10 amino
            (B) TYPE: amino acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear
-      (ii) MOLECULE TYPE: peptide
-      (ix) FEATURE:
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            (B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#D              /label=
#"D isomer of phenylalanine"
-      (ix) FEATURE:
            (A) NAME/KEY:.  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids      (A) LENGTH: 10 amino
            (B) TYPE: amino acid
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          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear
-     (ii) MOLECULE TYPE: peptide
-     (ix) FEATURE:
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          (B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#D             /label=
#"D isomer of phenylalanine"
-     (ix) FEATURE:
          (A) NAME/KEY:.  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids    (A) LENGTH: 10 amino
          (B) TYPE: amino acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear
-     (ii) MOLECULE TYPE: peptide
-     (ix) FEATURE:
          (A) NAME/KEY: Modified-sit - #e
          (B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#D             /label=
#"D isomer of phenylalanine"
-     (ix) FEATURE:
          (A) NAME/KEY:.  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids    (A) LENGTH: 10 amino
          (B) TYPE: amino acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear
-     (ii) MOLECULE TYPE: peptide
-     (ix) FEATURE:
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          (B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#D             /label=
#"D isomer of phenylalanine"
-     (ix) FEATURE:
          (A) NAME/KEY:.  .  .
DETD   .  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids    (A) LENGTH: 10 amino
          (B) TYPE: amino acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear
-     (ii) MOLECULE TYPE: peptide
-     (ix) FEATURE:
          (A) NAME/KEY: Modified-sit - #e
          (B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#D             /label=
#"D isomer of phenylalanine"
-     (ix) FEATURE:
          (A) NAME/KEY:.  .  .  (i) SEQUENCE CHARACTERISTICS:
#acids    (A) LENGTH: 10 amino
          (B) TYPE: amino acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear
-     (ii) MOLECULE TYPE: peptide
-     (ix) FEATURE:
          (A) NAME/KEY: Modified-sit - #e
          (B) LOCATION: 1
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#/product= "OTHER"R INFORMATION:
#Phg /label=
#"Phenylglycine"note=
- (ix) FEATURE:
(A) NAME/KEY: Modified-sit - #e
. . . (i) SEQUENCE CHARACTERISTICS:
#acids (A) LENGTH: 10 amino
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (ix) FEATURE:
(A) NAME/KEY: Modified-sit - #e
(B) LOCATION: 1
#/product= "OTHER"R INFORMATION:
#Phg /label=
#"Phenylglycine"note=
- (ix) FEATURE:
(A) NAME/KEY: Modified-sit - #e
. . .

19. A peptide, comprising the modified Neuropeptide Y of claim 1, and a Neuropeptide Y unrelated amino acid segment, a pharmaceutically acceptable salt. . .

20. A composition, comprising the modified Neuropeptide Y of claim 1, and a carrier.

21. The composition of claim 8, wherein the carrier is a physiologically acceptable carrier.

22. The composition of claim 9, wherein the carrier is a pharmaceutically acceptable carrier.

27. The composition of claim 8, wherein the carrier is selected from the group consisting of solid and liquid carriers .

28. The composition of claim 8, further comprising an agent selected from the group consisting of other therapeutic agents, flavorings, lubricants, suspending and thickening agents, binders, inert diluents, surface active agents, dispersants, antioxidants, buffers, bacteriostats and solutes to attain isotonicity.

. . . A formulation, comprising the composition of claim 8, which is selected from the group consisting of inhalation, oral, rectal, topical, parenteral, and transdermal formulations.

35. The formulation of claim 30, which is a parenteral formulation.

36. The parenteral formulation of claim 35, comprising an injectable formulation.

. . . group consisting of sucrose, acacia and tragacanth; and pastilles further comprising an inert base selected from the group consisting of gelatin, glycerin, sucrose and acacia.

42. The parenteral formulation of claim 30, comprising a solution, suspension or emulsion.

. . . consisting of injectable solutions or suspensions, and which may further comprise an agent selected from the group consisting of antioxidants, buffers, bacteriostatic agents and solutes which render the solution or suspension isotonic with the blood of a recipient.

. . . selected from the group consisting of ointments, creams, lotions, pastes, gels, sprays, aerosols and oils; and may further comprise a carrier selected from the group consisting of vaseline, lanoline, polyethylene glycols, alcohols and trans-dermal enhancers.

. . . is an iontophoretic formulation selected from the group consisting of iontophoretic solutions and suspensions, and which may further comprise a buffer.

. . . composition of claim 30, wherein the flavoring and inert diluent are selected from the group consisting of sucrose, acacia, tragacanth, gelatin and glycerin.

59. The method of claim 58, wherein the agent is administered as a composition further comprising a pharmaceutically acceptable carrier.

62. The method of claim 58, wherein the agent is administered parenterally.